REVIEW

Personal Use of Hair Dyes and Risk of Cancer
A Meta-analysis

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Context Use of hair dyes has been suggested recently as a risk factor for several types of cancer in epidemiologic studies. This alarming news and controversial declarations by scientific organizations and general media have made necessary a systematic evaluation of the epidemiologic evidence.

Objective To examine the association between personal use of hair dyes and relative risk of cancer.

Data Sources We retrieved studies published in any language by systematically searching the MEDLINE (1966–January 2005), EMBASE, LILACS, and ISI Proceedings computerized databases and by manually examining the references of the original articles, reviews, and monographs retrieved.

Study Selection We included cohort and case-control studies reporting relative risk estimates and 95% confidence intervals (CIs) (or data to calculate them) of personal hair dye use and cancer. We excluded studies that dealt with occupational exposure. We carried out separate analyses for bladder, breast, and hematopoietic cancers and cancers of other sites. Seventy-nine studies were included of 210 articles identified in the search.

Data Extraction Data were extracted independently by 2 investigators. We used a standardized questionnaire to record information on study design, sample size, type of controls, year of publication, adjustment factors, and relative risks of cancer among ever users of hair dyes. When possible, we extracted association measures on use of permanent dyes and extensive use (>200 lifetime episodes of dye use).

Data Synthesis Study-specific relative risks were weighted by the inverse of their variance to obtain fixed- and random-effects pooled estimates. The pooled relative risk for ever users of hair dyes was 1.06 (95% CI, 0.95-1.18) for breast cancer (14 studies), 1.01 (95% CI, 0.89-1.14) for bladder cancer (10 studies), and 1.15 (95% CI, 1.05-1.27) for hematopoietic cancers (40 studies). Other cancers were examined by only 1 or 2 studies, of which the pooled or single relative risk was elevated for brain cancer, ovarian cancer, and cancer of the salivary glands. No effect was observed for use of permanent dyes or for extensive use.

Conclusions We did not find strong evidence of a marked increase in the risk of cancer among personal hair dye users. Some aspects related to hematopoietic cancer and other cancers that have shown evidence of increased risk in 1 or 2 studies should be investigated further.

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THERE IS GROWING CONCERN worldwide about a possible increase in the risk of cancer among users of hair dyes. Some aromatic amines contained in hair dyes are mutagenic in vitro[1] and are carcinogenic in animals and humans.[2,3] Prompted by the publication of a study that showed a positive relation between hair dyes and bladder cancer,[4] the Scientific Committee on Cosmetic Products and Non-food Products (European Commission) called for an urgent review of the information and concluded in 2004 that "bladder cancer may be caused by carcinogenic arylamines in the hair dye solutions."[5] The US Food and Drug Administration declared recently that "FDA continues to follow research in this field,"[6] while the International Agency for Research on Cancer has stated that there is "inadequate evidence of carcinogenicity" of hair dyes.[7] In 2002, the British Broadcasting Corporation (BBC) caused alarm by reporting that "the Cancer Research Society advised consumers not to use hair products until further research has been completed."[8] However, it was not possible to confirm the authorship and veracity of this declaration.

As indicated by these statements, health organizations are concerned about the carcinogenicity of hair dyes, although their position sways between skeptical vigilance and official calls for bans of these products.

An association between hair dyes and cancer would be an important public health concern since about one third of women in Europe and North America, along with 10% of men older than 40 years, use some type of hair dye.[9] Permanent dyes, the most aggressive type, represent 70% of the market share—even more in Asia.[7]

Recent reviews have commented on the association between dye use and cancer.[7,9-11] However, no meta-

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analysis has been carried out so far. We therefore summarized the scientific evidence following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for meta-analyses of observational studies.[12]

METHODS

Systematic Search

We conducted a computerized MEDLINE search from 1966 to January 2005 to identify potentially eligible studies. A study was defined as an analysis of a specific cancer-exposure association; thus, a single article or publication could report several studies. We applied the following algorithm both in Medical Subject Heading and in free-text words: (hair) and (dye* or colour* or color*) and (cancer* or neoplasm* or carcinogen*). To check whether every article on the topic was retrieved, we performed a second search, introducing the words *cancer*, *neoplasms*, and *hair dye* in an unstructured fashion. We used similar strategies to search EMBASE (1980-2004) and LILACS (Latin America and Caribbean) databases. We searched meeting abstracts using the ISI Proceedings database from its inception in 1990 to 2004. We also examined the references of every article retrieved and those of recent reviews and monographs of hair dyes and cancer.[9-11] We considered including any relevant article, independent of the lan-

Table 1. Study-Specific RRs of Female Breast Cancer and Hair Dye Use

Source	RR (95% CI)			Type of Controls	Adjustment, Matching, and Restriction Factors	Cases/Controls or Cohort Size
	Hair Dye (Any)	Permanent Dye	Intensive Exposure*			
Case-Control Studies						
Kinlen et al,[21] 1977	1.01 (0.71-1.44)	. . .	0.69 (019-2.25)	H	Age, marital status, social class	191/561
Shore et al,[22] 1979	0.98 (0.75-1.27)	1.04 (0.79-1.37)	1.28 (0.58-2.79)	H	Age, duration of hair dye use	129/193
Nasca et al,[23] 1980	1.28 (0.80-2.05)	. . .	1.70 (0.52-5.52)	P	Age, county of residence, unspecified others	118/233
Stavraky et al,[24,25] 1979, 1981 (Toronto)	1.1 (0.5-2.7)	1.1 (0.5-2.4)	. . .	P	Age, smoking, family history of cancer, age at first birth	35/70
Stavraky et al,[24,25] 1979, 1981 (London)	1.2 (0.6-2.6)	1.3 (0.6-2.5)	. . .	H	Age, smoking, family history of cancer, age at first birth	50/100
Wynder and Goodman,[26] 1983	1.02 (0.78-1.32)	. . .	1.18 (0.84-1.64)	H	Age, religion, education, marital status, smoking	401/625
Koenig et al,[27] 1991	0.8 (0.6-1.1)	0.85 (0.70-1.03)	0.8 (0.6-1.2)	H	Age, family history of cancer, age at first birth, birthplace, race, religion, history of receiving Medicaid	398/790
Nasca et al,[28] 1992	1.04 (0.90-1.21)	1.00 (0.86-1.17)	1.01 (0.82-1.24)	P	Age, county of residence	1617/1617
Boice et al,[29] 1995	1.08 (0.87-1.33)	. . .	. . .	P	Age, age at menarche, menopause, and first birth, family history of breast cancer	528/2628
Cook et al,[30] 1999	1.3 (1.0-1.6)	1.00 (0.7-1.3)	. . .	P	Age, parity, weight, income, education, marital status, family history of breast cancer, smoking, alcohol consumption	844/960
Zheng et al,[31] 2002	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.9 (0.9-4.0)	P	Age, race, menopause, study site, history of breast cancer, history of lactation, fat intake	608/609
Petro-Nustas et al,[32] 2002	8.62 (3.33-22.28)	. . .	. . .	P	Age, parity, education, place of residence	100/100
Cohort Studies						
Green et al,[33] 1987	. . .	1.1 (0.9-1.2)	0.98 (0.71-1.37)	. . .	Age, age at first birth, smoking, history of breast cancer, menopausal status, history of benign breast disease	353/118 404
Altekruse et al,[34] 1999	. . .	0.9 (0.9-1.0)	0.9 (0.8-1.1)	. . .	Age, race, duration of hair dye use, smoking	782/547 589†

Abbreviations: CI, confidence interval; H, hospital; P, population; RR, relative risk. Ellipses indicate data not applicable.
*Defined as more than 200 lifetime exposures to hair dye.
†Based on fatal cancer cases.

guage of the publication. Unpublished studies were not considered. Formal translation was necessary in only 1 article published in Japanese.[13] All searches were carried out independently by 2 epidemiologists (B.T. and A.M.-M.) and results were merged.

Inclusion Criteria and Data Collection

Studies were included if (1) they presented original data from case-control or cohort studies; (2) the outcome of interest was clearly defined as cancer of an anatomical site; (3) the exposure of interest was personal hair dye use; and (4) they provided relative risk (RR) estimates and their confidence intervals (CIs) or provided enough data to calculate them (raw data, *P* value, or variance estimate). We did not consider studies that dealt with occupational exposure to hair dyes or those that concerned childhood cancers related to use of hair dye by the mother. If data were duplicated in more than 1 study, the most recent study was included in the analysis. We contacted the authors of the publications when further explanations were necessary to assess whether the information provided in more than 1 article concerned the same study. When RRs of cancer of different anatomical sites were available in the same publication, we considered each cancer separately.

We developed a questionnaire and recorded study name, year of publication, study design, sample size (cases and controls or cohort size), type of controls for case-control studies (patients with other diseases or population-based controls), variables used for adjustment or matching, and association measures that compared ever users of hair dyes with never users for any (or unspecified) type of dye. When available, we also extracted association measures and CIs corresponding to the exclusive use of permanent dye and carried out a separate analysis for this type of dye. If a study provided information on permanent dye only and not on use of hair dye of any kind, we included this information in the pooled analysis of hair dye of any type. To check for possible changes in the result, we later recalculated our pooled estimate for hair dye of any type excluding studies that provided information on permanent dye only. Results

Table 2. Pooled RRs of Female Breast Cancer and Hair Dye Use

	No. of Studies	Fixed-Effects RR (95% CI)	Random-Effects RR (95% CI)	R_i*	*P* Value (by Q Test)
All studies (any dye use)	14	1.04 (0.98-1.09)	1.06 (0.95-1.18)	0.68	<.001
Cohort studies	2	1.01 (0.95-1.08)	1.00 (0.82-1.21)	0.88	.002
Case-control studies	12	1.07 (0.98-1.15)	1.09 (0.94-1.25)	0.62	.003
Population-based	7	1.12 (1.01-1.23)	1.21 (0.96-1.52)	0.77	.001
Hospital-based	5	0.96 (0.84-1.11)	0.96 (0.84-1.11)	0.00	.76
Permanent dye use only	9	1.00 (0.94-1.05)	0.98 (0.91-1.07)	0.40	.13
Intensive exposure†	9	0.99 (0.89-1.11)	0.99 (0.89-1.11)	0.00	.45

Abbreviations: CI, confidence interval; RR, relative risk.
*Proportion of total variance due to between-study variance.
†Defined as more than 200 lifetime exposures to hair dye.

Table 3. Study-Specific RRs of Bladder Cancer and Hair Dye Use

Source	RR (95% CI)			Type of Controls	Adjustment, Matching, and Restriction Factors	Cases/Controls or Cohort Size
	Hair Dye (Any)	Permanent Dye	Intensive Exposure*			
Case-Control Studies						
Jain et al,[35] 1977	1.1 (0.41-3.03)	. . .	. . .	H	Age, sex	107/107
Neutel et al,[36] 1978	0.92 (0.38-2.24)	. . .	. . .	H	Age, sex	50/50
Howe et al,[37] 1980	0.7 (0.3-1.4)	. . .	. . .	P	Age, sex	632/632
Stavraky et al,[25] 1981	1.1 (0.4-2.8)	. . .	. . .	P	Sex, unspecified others	23/46
Hartge et al,[14] 1982	1.0 (0.9-1.2)	. . .	0.82 (0.65-1.03)	P	Age, sex, race, smoking	2982/5782
Ohno et al,[38] 1985	1.49 (0.89-2.5)	. . .	. . .	P	Age, sex, smoking	293/589
Nomura et al,[39] 1989	1.41 (0.86-2.33)	. . .	. . .	P	Age, sex, race, place of residence, smoking	261/522
Gago-Dominguez et al,[4] 2001	1.0 (0.7-1.4)	1.3 (0.8-2.0)	1.83 (1.18-2.84)	P	Age, sex, race, place of residence, smoking	897/897
Andrew et al,[40] 2004	0.70 (0.49-1.00)	1.15 (0.70-1.88)	1.9 (0.7-4.8)	P	Age, sex, smoking, education level	495/665
Cohort Study						
Henley and Thun,[41] 2001	. . .	1.08 (0.84-1.38)	. . .	. . .	Age, sex, race, smoking, education, occupation	336/547 571†

Abbreviations: CI, confidence interval; H, hospital; P, population; RR, relative risk. Ellipses indicate data not applicable.
*Defined as more than 200 lifetime exposures to hair dye.
†Based on fatal cancer cases.

were similar in both analyses, so only the former was presented in the tables. When possible, we also extracted RRs for intensive use of hair dye, defined as 200 or more lifetime episodes of dyeing. If not directly available in the publications, we calculated this magnitude assuming an average frequency of hair dyeing of 11.7 times per year among women. This number was obtained from the distribution of hair dye use among the control group of 1 of the studies included in our meta-analysis, which provided detailed information on frequency of use.[14]

Quality Assessment

We assessed study quality based on a 10-point scale that included elements of previous published scales adapted to the needs of the present meta-analysis.[15] Each study was scored according to 5 characteristics of methods and presentation of results. Each item was scored from 0 to 2. Specifically, for case-control studies, we determined whether participation rate was at least 80% in both groups; whether cases were incident, prevalent, or dead; whether controls were taken from 1 or various hospitals or from the general population; whether potential confounding for sex, age, and smoking was corrected or prevented through matching or adjustment; and whether duration of exposure to hair dye was accurately measured. For cohort studies, in addition to the criteria listed above that were not specific to case-control designs, we determined whether loss to follow-up was less than 20% of the initial cohort size and whether efforts were made to ensure that the cohort did not change exposure during follow-up. (The complete protocol for quality scoring is available on request from the authors.) For stratification purposes, studies that scored 7 or higher of 10 were considered to be of high quality and the rest to be of low quality. Quality scoring was performed independently by 2 reviewers (B.T. and A.M.-M.) and the average score between reviewers was assigned to the studies. Disagreement was measured by the Bland-Altman limits-of-agreement method.[16] The average disagreement was close to zero (–0.22; 95% CI, –2.42 to 1.98). The fact that the 95% CI is symmetric around zero suggests that there was no systematic disagreement.

Table 4. Pooled RRs of Bladder Cancer and Hair Dye Use

	No. of Studies	Fixed-Effects RR (95% CI)	Random-Effects RR (95% CI)	R_i*	*P* Value (by Q Test)
All studies (any dye use)	10	1.01 (0.89-1.14)	1.01 (0.89-1.14)	0.05	.41
Case-control studies	9	0.99 (0.87-1.13)	0.99 (0.85-1.15)	0.14	.35
Population-based	7	0.99 (0.87-1.13)	1.00 (0.83-1.20)	0.38	.15
Hospital-based	2	0.82 (0.47-1.43)	0.82 (0.47-1.43)	0.00	.42
Permanent dye use only	3	1.13 (0.93-1.38)	1.13 (0.93-1.38)	0.00	.78
Intensive exposure†	3	1.00 (0.82-1.22)	1.33 (0.69-2.56)	0.90	.001

Abbreviations: CI, confidence interval; RR, relative risk.
*Proportion of total variance due to between-study variance.
†Defined as more than 200 lifetime exposures to hair dye.

Statistical Analysis

We weighted the study-specific adjusted log odds ratios for case-control studies and log RRs for cohort studies by the inverse of their variance to compute a pooled RR and its 95% CI. We presented both fixed- and random-effects pooled estimates but preferentially used the latter when heterogeneity was present.

We used a parametric bootstrap version (1000 replications) of the DerSimonian and Laird Q test to check for heterogeneity.[17] The null hypothesis of this test is absence of heterogeneity. To quantify this heterogeneity, we calculated the proportion of the total variance due to between-study variance (R_i statistic).[17] To further explore the origin of heterogeneity, we restricted the analysis to subgroups of studies defined by study characteristics such as case-control/cohort design, adjustment factors, and type of controls (hospital-based or population-based).

We used funnel plots to assess publication bias visually. Because funnel plots have several limitations and represent only an informal way to detect publication bias,[18] we carried out more formal testing using the test proposed by Egger et al.[19] All analyses were performed with the software HEpiMA, version 2.1.3,[20] and STATA, version 8.0 (Stata Corp, College Station, Tex).

RESULTS

We identified 79 studies, carried out in 11 countries, on personal hair dye use and cancer that met our inclusion criteria and were included in the analysis.

We found 14 studies on breast cancer,[21-34] 10 studies on bladder cancer,[4,14,25,35-41] and 40 studies on hematopoietic cancers.[25,34,42-58] Furthermore, 2 studies provided data on adult brain tumors,[59,60] 2 on skin cancer,[61-63] 2 on ovarian cancer,[25,64] and 2 on cervical cancer.[25,51] We also found 1 study for each of the following cancer sites: salivary gland,[65] endometrium,[25] vagina,[51] oral cavity,[51] soft tissue sarcoma,[58] digestive system,[51] and respiratory system.[51]

Among the studies that could have been relevant to our meta-analysis, 1 was excluded because it presented cross-sectional data[66] and another because it did not present any measure of uncertainty of the RR.[67]

Breast Cancer

The 12 case-control studies (involving 5019 cases and 8486 controls) and 2 cohort studies that dealt with breast cancer were published between 1977 and 2002 (TABLE 1). Seven case-control studies used population-based controls and 5 used hospital-based controls.

Compared with never use of hair dyes, the random-effects pooled RR of breast cancer for any type of dye use was 1.06 (95% CI, 0.95-1.18). The pooled RR for exclusive use of permanent dye was 1.00 (95% CI, 0.94-1.05) and was 0.99 (95% CI, 0.89 to 1.11) for intensive exposure (TABLE 2). There was no substantial difference in pooled RRs

Table 5. Study-Specific RRs of Hematopoietic Cancers and Hair Dye Use

Source	RR (95% CI)			Type of Controls	Adjustment, Matching, and Restriction Factors	Cases/Controls or Cohort Size
	Hair Dye (Any)	Permanent Dye	Intensive Exposure*			
Non-Hodgkin Lymphoma						
Case-control studies						
Stavraky et al,[25] 1981†						
Toronto	0.7 (0.3-1.6)	. . .	. . .	P	Sex, unspecified others	45/90
London	1.2 (0.4-3.8)	. . .	. . .	H	Sex, unspecified others	25/50
Cantor et al,[42] 1988‡	2.0 (1.3-3.0)	. . .	. . .	P	Age, sex, place of residence, smoking, pesticide exposure, family history of cancer	53/1245
Zahm et al,[43] 1992‡	1.29 (0.93-1.81)	1.7 (1.1-2.8)	1.2 (0.6-2.7)	P	Age, sex, race, vital status	385/1432
Linos et al,[44] 1994	2.07 (0.79-5.41)	. . .	2.07 (0.79-5.41)	H	Age, sex	179/274
Holly et al,[45] 1998	1.07 (0.86-1.34)	0.85 (0.61-1.19)	1.0 (0.7-1.6)	P	Age, sex, sexual preference, number of sexual partners, smoking, education	1593/2515
Miligi et al,[46] 1999‡	1.0 (0.8-1.2)	. . .	. . .	P	Age, sex, education, smoking	611/828
Schroeder et al,[47] 2002	2.0. (1.3-2.9)	. . .	. . .	P	Age, sex, residency, vital status	182/1245
Zhang et al,[48] 2004	1.1 (0.9-1.5)	1.2 (0.9-1.5)	1.18 (0.85-1.63)	P	Age, sex, family history of cancer, race, education, smoking, alcohol consumption	449/519
Chiu et al,[49] 2004						
Iowa	1.99 (1.29-3.06)	. . .	. . .	P	Age, sex, race, place of residence, vital status	605/1206
Nebraska	0.90 (0.47-1.71)	. . .	. . .	P	Age, sex, race, place of residence, vital status	200/712
Tavani et al,[58] 2005‡	1.03 (0.73-1.44)	1.25 (0.87-1.79)	. . .	H	Age, sex, place of residence, smoking, education	446/1295
Cohort studies						
Grodstein et al,[50] 1994	. . .	1.1 (0.8-1.6)	0.9 (0.5-1.7)	. . .	Age, sex, smoking	144/99 067
Altekruse et al,[34] 1999	. . .	1.1 (1.0-1.3)	1.0 (0.8-1.3)	. . .	Age, sex, race, duration of dye use, smoking	350/573 369§
Hodgkin Disease						
Case-control studies						
Zahm et al,[43] 1992‡	1.7 (0.8-3.5)	3.2 (1.3-8.2)	5.0 (0.5-40.2)	P	Age, sex, race, vital status	70/1418
Tavani et al,[58] 2005‡	0.68 (0.40-1.18)	1.14 (0.63-2.08)	. . .	H	Age, sex, place of residence, smoking, education	158/1295
Cohort studies						
Grodstein et al,[50] 1994	. . .	0.9 (0.4-2.1)	. . .	. . .	Age, sex, smoking	24/99 067
Thun et al,[51] 1994	0.55 (0.23-1.36)	. . .	. . .	. . .	Age, sex, race, smoking	31/573 369§
Multiple Myeloma						
Case-control studies						
Zahm et al,[43] 1992‡	1.8 (1.0-3.3)	3.2 (1.3-7.9)	1.0 (0.1-5.0)	P	Age, sex, race, vital status	69/1418
Brown et al,[52] 1992	1.9 (1.0-3.6)	. . .	. . .	P	Age, sex, vital status	173/650
Herrinton et al,[53] 1994	1.14 (0.87-1.50)	. . .	. . .	P	Age, sex, race, study center, education	689/1681
Tavani et al,[58] 2005‡	1.17 (0.70-1.97)	1.28 (0.75-2.19)	. . .	H	Age, sex, place of residence, smoking, education	141/1295
Cohort studies						
Grodstein et al,[50] 1994	. . .	0.4 (0.2-0.9)	. . .	. . .	Age, sex, smoking	32/99 067
Altekruse et al,[34] 1999	. . .	1.0 (0.8-1.3)	1.0 (0.7-1.5)	. . .	Age, sex, race, duration of dye use, smoking	131/573 369§

(continued)

across designs (cohort, hospital-based case-control, and population-based case-control studies). Restricting the analysis to the 7 studies that scored 7 points or higher on the quality scale did not alter the results (RR, 1.06; 95% CI, 0.93-1.20). Heterogeneity of the study-specific RRs was moderate to large for case-control studies (R_i=0.62) and all studies analyzed together (R_i=0.68). This was explained mainly by the result of 1 population-based case-control study[32] with an RR of 8.62 and a wide 95% CI, which might be considered as an influential point. Exclud-

Table 5. Study-Specific RRs of Hematopoietic Cancers and Hair Dye Use (cont)

Source	RR (95% CI) Hair Dye (Any)	Permanent Dye	Intensive Exposure*	Type of Controls	Adjustment, Matching, and Restriction Factors	Cases/Controls or Cohort Size
			Leukemia			
Case-control studies						
Cantor et al,[42] 1988‡						
Acute nonlymphocytic	1.1 (0.5-2.6)	. . .	. . .	P	Age, sex, place of residence, smoking, pesticide exposure, family history of cancer	143/1245
Acute lymphocytic	2.9 (0.4-13.8)	. . .	. . .	P	Age, sex, place of residence, smoking, pesticide exposure, family history of cancer	16/1245
Chronic lymphocytic	1.4 (0.7-2.6)	. . .	. . .	P	Age, sex, place of residence, smoking, pesticide exposure, family history of cancer	243/1245
Chronic myeloid	2.2 (0.7-6.2)	. . .	. . .	P	Age, sex, place of residence, smoking, pesticide exposure, family history of cancer	51/1245
Other leukemia	3.3 (1.4-7.6)	. . .	. . .	P	Age, sex, place of residence, smoking, pesticide exposure, family history of cancer	61/1245
Zahm et al,[43] 1992 (chronic lymphocytic)‡	1.0 (0.5-2.2)	0.8 (0.1-4.0)	. . .	P	Age, sex, race, vital status	56/1418
Mele et al,[54] 1994‡						
Acute myeloid	1.01 (0.78-1.30)	. . .	. . .	H	Age, sex, education, place of residence	252/1161
Acute lymphocytic	1.2 (0.8-1.8)	. . .	. . .	H	Age, sex, education, place of residence	100/1161
Chronic myeloid	1.1 (0.75-1.60)	. . .	. . .	H	Age, sex, education, place of residence	156/1161
Markovic-Denic et al,[55] 1995 (chronic lymphocytic)	1.97 (1.08-3.59)	. . .	. . .	H	Age, sex, place of residence	130/130
Miligi et al,[46] 1999 (all leukemia)‡	0.9 (0.7-1.3)	. . .	. . .	P	Age, sex, education, smoking	260/828
Bjork et al,[56] 2001 (chronic myeloid)	0.35 (0.18-0.68)	. . .	. . .	P	Age, sex, place of residence	255/765
Rauscher et al,[57] 2004 (acute)	1.3 (1.0-1.8)	1.6 (1.1-2.4)	1.00 (0.5-2.0)	P	Age, sex, race, education, place of residence	769/623
Cohort studies						
Grodstein et al,[50] 1994						
Chronic lymphocytic	. . .	0.6 (0.3-1.5)	. . .	. . .	Age, sex, smoking	23/99 067
Acute and chronic myeloid and acute lymphocytic	. . .	0.8 (0.3-1.9)	. . .	. . .	Age, sex, smoking	21/99 067
Altekruse et al,[34] 1999 (all leukemia)	. . .	1.1 (0.9-1.3)	1.3 (1.0-1.7)	. . .	Age, sex, race, duration of dye use, smoking	718/573 369§

Abbreviations: CI, confidence interval; H, hospital; P, population; RR, relative risk. Ellipses indicate data not applicable.
*Defined as more than 200 lifetime exposures to hair dye.
†Cases are reported as "lymphoma and leukemia" cases in the original study.
‡These studies used the same control group for several outcomes.
§Based on fatal cancer cases.

ing this study resulted in low heterogeneity (R_i=0.36). The funnel plot did not provide evidence for publication bias (data not shown). The Egger test of asymmetry of the funnel plot yielded a *P* value of .90, which did not change substantially when the outlier was excluded (*P*=.72).

Bladder Cancer

The 10 studies, presented in TABLE 3, that provided data on bladder cancer (9 case-control studies comprising 5740 cases and 9290 controls and 1 cohort study with 336 cases) did not show substantial heterogeneity. The only exception was for intensive exposure, the heterogeneity of which was high but based on only 3 studies.

The pooled RR (TABLE 4) did not show any effect of hair dye on bladder cancer (RR, 1.01; 95% CI, 0.89-1.14 for all studies). This absence of effect was constant across study designs, types of exposure (permanent dyes and inten-

sive exposure), and sex (RR, 1.03; 95% CI, 0.90-1.17 for women and RR, 0.93; 95% CI, 0.77-1.13 for men). Since smoking is an important risk factor for bladder cancer, we recalculated our pooled estimates for studies that provided data explicitly adjusted for tobacco consumption.[4,14,38-41] The pooled RR was 1.05 (95% CI, 0.93-1.19).

Stratifying the analysis by quality scoring did not show any difference in the pooled RRs between studies with good quality scores and the remainder. We could not detect any evidence of publication bias on the funnel plot (P=.75 by Egger symmetry test).

Hematopoietic Cancers

TABLE 5 and TABLE 6 show the specific RRs for the 40 studies that dealt with hematopoietic cancers and the pooled RRs for different types of these cancers. When all hematopoietic cancers were analyzed together, we observed a borderline increase in the risk (RR, 1.15; 95% CI, 1.05-1.27) for ever users of hair dye. This increase is restricted to case-control studies (RR, 1.23; 95% CI, 1.09-1.39) and, more specifically, to the 17 case-control studies with data on men (RR, 1.57; 95% CI, 1.33-1.84). No cohort study with data on men was available for comparison. In these categories, heterogeneity was large. On the contrary, we did not observe any risk increase when we restricted our analysis to women (RR, 1.04; 95% CI, 0.97-1.11), to exclusive use of permanent dyes (random-effects RR, 1.14; 95% CI, 0.99-1.29), or to intensive exposure to hair dyes. Stratification by quality scoring or by adjustment for smoking did not pro-

Table 6. Pooled RRs of Hematopoietic Cancers and Hair Dye Use

	No. of Studies	Fixed-Effects RR (95% CI)	Random-Effects RR (95% CI)	R_i*	P Value (by Q Test)
Non-Hodgkin lymphoma					
All studies (any dye use)	14	1.16 (1.07-1.26)	1.23 (1.07-1.42)	0.57	.008
Cohort studies	2	1.10 (0.94-1.28)	1.10 (0.94-1.28)	0.00	.99
Case-control studies	12	1.19 (1.08-1.32)	1.27 (1.06-1.53)	0.63	.002
Population-based	9	1.20 (1.08-1.33)	1.29 (1.04-1.59)	0.72	<.001
Hospital-based	3	1.31 (1.18-1.45)	1.31 (1.18-1.45)	0.00	.63
Permanent dye use only	6	1.13 (1.01-1.26)	1.13 (0.99-1.29)	0.19	.32
Intensive exposure†	6	1.07 (0.90-1.28)	1.07 (0.90-1.28)	0.00	.72
Hodgkin disease					
All studies (any dye use)	4	0.87 (0.61-1.24)	0.88 (0.54-1.42)	0.42	.17
Permanent dye use only	3	1.34 (0.86-2.06)	1.41 (0.72-2.77)	0.57	.11
Multiple myeloma					
All studies (any dye use)	6	1.11 (0.95-1.31)	1.14 (0.86-1.52)	0.62	.04
Cohort studies	2	0.92 (0.71-1.18)	0.69 (0.28-1.66)	0.91	.004
Case-control studies	4	1.28 (1.04-1.59)	1.31 (1.03-1.67)	0.17	.33
Permanent dye use only	4	1.04 (0.84-1.30)	1.10 (0.62-1.95)	0.83	.003
Leukemia					
All studies (all leukemia types, any dye use)	16	1.10 (1.00-1.22)	1.12 (0.94-1.34)	0.54	.01
All leukemia types, studies with different sets of controls only	8	1.06 (0.94-1.21)	0.97 (0.74-1.28)	0.71	.01
Cohort studies (all leukemia types)	3	1.07 (0.91-1.25)	1.05 (0.87-1.28)	0.16	.34
Case-control studies (all leukemia types)	13	1.13 (0.99-1.28)	1.19 (0.95-1.49)	0.59	.004
Acute leukemia	5	1.14 (0.96-1.36)	1.14 (0.96-1.36)	0.00	.56
Chronic leukemia	6	1.11 (0.89-1.40)	1.13 (0.69-1.86)	0.76	.003
Myeloid leukemia	5	0.99 (0.82-1.18)	0.94 (0.64-1.39)	0.73	.02
Lymphocytic leukemia	5	1.41 (1.06-1.88)	1.41 (1.06-1.88)	0.00	.56
Permanent dye use only	5	1.13 (0.97-1.31)	1.12 (0.86-1.46)	0.48	.23
All hematopoietic cancers					
All studies	40	1.13 (1.06-1.20)	1.15 (1.05-1.27)	0.52	<.001
Studies with different sets of controls only	22	1.12 (1.04-1.21)	1.11 (0.97-1.28)	0.60	<.001
Cohort studies	9	1.04 (0.94-1.15)	1.01 (0.89-1.16)	0.25	.27
Case-control studies	31	1.17 (1.09-1.26)	1.23 (1.09-1.39)	0.55	<.001
Male-only studies	17	1.57 (1.33-1.84)	1.56 (1.32-1.85)	0.04	.43
Permanent dye use (all)	18	1.12 (1.04-1.22)	1.14 (0.99-1.29)	0.44	.03
Studies with different sets of controls	11	1.08 (0.99-1.18)	1.06 (0.94-1.20)	0.35	.15
Intensive exposure (all)†	11	1.12 (0.98-1.28)	1.12 (0.98-1.28)	0.00	.76
Studies with different sets of controls†	8	1.11 (0.97-1.27)	1.11 (0.97-1.27)	0.00	.69

Abbreviations: CI, confidence interval; RR, relative risk.
*Proportion of total variance due to between-study variance.
†Defined as more than 200 lifetime exposures to hair dye.

duce any change in the results. The funnel plot showed substantial asymmetry (data not shown), confirmed by statistical testing (*P* value of the intercept=.02 by Egger test). Apparently, there is a deficit of studies that show a slightly protective but imprecise effect in their results. Our calculations show that only 5 such unpublished case-control studies, with an RR of 0.8 and a 95% CI of 0.6 to 1.1, would be sufficient to cancel the association between hair dye use and risk of hematopoietic cancers and render it nonsignificant (RR, 1.09; 95% CI, 0.99-1.20).

Separate analyses by cancer site show a slight increase in the risk of non-Hodgkin lymphoma for ever users of hair dye (RR, 1.23; 95% CI, 1.07-1.42), which seems to be restricted to case-control studies. However, the results of intensive exposure do not show any association.

Case-control studies of multiple myeloma and lymphocytic leukemia show a slight increase of the risk.

Other Cancers

TABLE 7 presents the study-specific RRs of other cancer sites for hair dye users vs never users. The single study on cancers of salivary glands shows a 3-fold increase of the risk.[65] The pooled RRs of the 2 studies available for each site were 1.83 (95% CI, 1.16-2.89) for brain tumors, 1.71 (95% CI, 1.15-2.53) for ovarian cancer, 0.74 (95% CI, 0.51-1.07) for skin cancer, and 0.89 (95% CI, 0.53-1.9) for cervical cancer.

COMMENT

Our results indicate that, globally, there is no effect of personal hair dye use on the risk of breast and bladder cancer.

There is a borderline effect for hematopoietic cancers. However, the evidence of a causal effect is too weak to represent a major public health concern. The fact that the restriction of the analysis to intensive exposure to hair dyes and to exclusive use of perma-

Table 7. Study-Specific RRs of Other Cancers and Hair Dye Use

Source	Type of Cancer	Type of Study	RR (95% CI)			Adjusted, Matching, or Restriction Factors	Cases/Controls or Cohort Size
			Hair Dye (Any)	Permanent Dye	Intensive Exposure*		
Ahlbom et al,[59] 1986	Brain	Case-control	1.5 (0.6-3.7)	. . .	. . .	Age, sex, place of residence	78/289
Burch et al,[60] 1987	Brain	Case-control	1.96 (1.15-3.32)	. . .	. . .	Age, sex, place of residence, marital status, diagnosis date	228/247
Holman and Armstrong,[61,62] 1983, 1985	Skin	Case-control	2.40 (0.92-6.28)	1.1 (0.8-1.6)	. . .	Age, sex, birth place, sunlight exposure	507/511
Osterlind et al,[63] 1988	Skin	Case-control	0.6 (0.5-0.9)	0.6 (0.4-1.0)	. . .	Age, sex	474/926
Stavraky et al,[25] 1981	Ovary	Case-control	0.91 (0.36-2.31)	. . .	. . .	Unspecified	58/116
Tzonou et al,[64] 1993	Ovary	Case-control	1.96 (1.27-3.03)		. . .	Age, age at menarche, at menopause, at first birth, education, smoking, alcohol consumption	189/200
Stavraky et al,[25] 1981	Cervix	Case-control	0.7 (0.3-1.9)	. . .	. . .	Unspecified others	38/76
Thun et al,[51] 1994	Cervix	Cohort	0.97 (0.53-1.77)	. . .	1.51 (0.63-3.59)	Age, race, smoking	Unspecified/573 369
Stavraky et al,[25] 1981	Endometrium	Case-control	1.6 (0.6-4.0)	. . .	. . .	Unspecified	36/72
Spitz et al,[65] 1990	Salivary gland	Case-control	3.01 (1.18-7.69)	. . .	3.5 (0.9-12.8)	Age, sex, race	64/128
Thun et al,[51] 1994	Vagina	Cohort	0.93 (0.43-2.03)	. . .	0.82 (0.19-3.47)	Age, race, smoking	Unspecified/573 369
Thun et al,[51] 1994	Oral cavity	Cohort	0.61 (0.32-1.14)	. . .	0.31 (0.07-1.25)	Age, sex, race, smoking	Unspecified/573 369
Thun et al,[51] 1994	Digestive system	Cohort	0.94 (0.85-1.03)	. . .	1.05 (0.90-1.23)	Age, sex, race, smoking	Unspecified/573 369
Thun et al,[51] 1994	Respiratory system	Cohort	1.00 (0.91-1.11)	. . .	1.20 (1-02-1.42)	Age, sex, race, smoking	Unspecified/573 369
Tavani et al,[58] 2005	Soft tissue sarcoma	Case-control	0.73 (0.45-1.17)	1.23 (0.75-2.00)	. . .	Age, sex, place of residence, smoking, education	221/1295

Abbreviations: CI, confidence interval; RR, relative risk.
*Defined as more than 200 lifetime exposures to hair dye.

nent hair dye does not strengthen the risk further is consistent with the absence of causal effect. Furthermore, there is room for publication bias as shown by the funnel plot, the result of the corresponding hypothesis test, and the fact that only a small number of negative studies, unpublished so far, would cancel the association. Nonetheless, the intriguing risk increase for male users of hair dyes deserves further consideration.

A plausible explanation for the lack of effect may be the low concentration of potential carcinogens in the hair dyes and the fact that the use of some dye ingredients, such as 2,4-diaminotoluene and 2,4-diaminoanisole, was discontinued in the mid 1970s after they were found to be carcinogenic in rodents.[7] The overwhelming majority of the studies were carried out several years after this ban went into effect.

There is potential for recall bias from case-control studies, which represent the majority of the studies included in this meta-analysis. However, the effect produced by this bias would be an exaggeration of the effect. Presence of misclassification bias of the exposure to hair dyes is not unlikely. Because exposure is generally measured at baseline and may change during follow-up, the potential for misclassification is higher for cohort studies, as mentioned by Miller and Bartsch.[68] If exposure is measured on a dichotomous scale (exposed vs nonexposed), the consequence of nondifferential misclassification would be to bias the estimates toward the absence of effect. However, globally in our meta-analysis, we did not detect substantial differences between pooled results from case-control and cohort studies.

One possible limitation of our meta-analysis is that several case-control studies use the same comparison group for different outcomes and, therefore, might not be considered as completely independent. This raises a multiple comparison issue that would result in finding more statistically significant associations than they actually exist.[42] This is particularly true for hematopoietic cancers because in several studies, the same control population was used to calculate relative risks for Hodgkin and non-Hodgkin lymphoma, leukemia, and multiple myeloma (Table 5).[42,43,46,54,58] This may partially explain the positive results for hematopoietic cancers. However, it should be noted that pooling results from studies that share the same control group should yield similar results as pooling results from studies that use independent control groups, provided that controls are selected independent of the exposure. Restricting our analysis to studies that used different comparison sets yielded identical results (Table 6).

Another possible limitation is that individual studies may have failed to control for potential known or unknown confounders or to take into account potential effect modifiers. A study has shown that bladder cancer among hair dye users is restricted to the specific genotype/phenotype of slow acetylators of N-acetyltransferase, an enzyme involved in the detoxification of aromatic amines.[4] This and other genetic factors are potential effect modifiers that were not addressed in the individual studies. Furthermore, it is remarkable that fewer than half of the studies explicitly adjusted for smoking, an established risk factor for cancer, although some authors decided not to adjust for it after having ruled out confounding in their data. Failure to adjust for confounders may bias the results in either direction, toward exaggeration or underestimation of the effect of personal hair dyes on cancer.

The borderline effect observed for brain tumors and ovarian cancer is based on the pooling of only 2 studies and does not permit a meaningful assessment of the risk. However, these results are based on reasonably sized case-control studies, although largely prone to bias (large proportion of proxy respondents,[60] large number of dead cases,[60] and imprecise exposure assessment[59]). Future studies may shed more light on the effect of hair dyes on these types of tumors.

In conclusion, we did not find strong evidence of a marked increase in the risk of cancer among personal hair dye users. Some aspects related to hematopoietic cancer should be investigated further. Efforts should be targeted toward the assessment of the risk of cancer in occupational settings where exposure to hair dyes is more prolonged and has a higher concentration and frequency than personal exposure.

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Study concept and design: Takkouche, Etminan.
Acquisition of data: Takkouche, Montes-Martinez.
Analysis and interpretation of data: Takkouche, Etminan, Montes-Martinez.
Drafting of the manuscript: Takkouche, Montes-Martinez.
Critical revision of the manuscript for important intellectual content: Etminan.
Statistical analysis: Takkouche, Etminan, Montes-Martinez.
Administrative, technical, or material support: Montes-Martinez.
Study supervision: Takkouche.
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